

# The Clinical Benefits of Dutasteride Treatment for LUTS and BPH

Claus G. Roehrborn, MD

Department of Urology, The University of Texas Southwestern Medical Center at Dallas, Dallas, TX

*Dutasteride is the first dual inhibitor of both 5 $\alpha$ -reductase Types 1 and 2 isoenzymes, with efficacy and safety proven in 3 randomized placebo-controlled trials, each 2 years in duration. The current report demonstrates that longer-term treatment over 48 months with dutasteride results in continuing improvements in urinary symptoms and flow rate, and further reductions in total and transition zone volume of the prostate in men with symptomatic benign prostatic hyperplasia (BPH). The reduction in risk of acute urinary retention and BPH-related surgery, seen in the double-blind phase, was durable over the 4-year term of the studies. The incidence of new onset adverse events remained low during the open-label extension phase, and less than 1% of patients discontinued therapy due to adverse events. These findings combined establish that the disease-modifying benefits of dutasteride are durable in long-term treatment. Dutasteride was also well tolerated in long-term use, with no new safety issues emerging over 4 years of treatment.*  
[Rev Urol. 2004;6(suppl 9):S22-S30]

© 2004 MedReviews, LLC

**Key words:** Benign prostatic hyperplasia • Lower urinary tract symptoms • 5 $\alpha$ -reductase inhibitors • Dutasteride • Clinical trials

Lower urinary tract symptoms (LUTS) are very common in aging men as well as women. In men, they are most often associated with the histologic presence of benign prostatic hyperplasia (BPH). Although BPH as a histologic diagnosis is clinically less relevant, when associated with irritative and obstructive LUTS symptomatology, it becomes a very bothersome condition.<sup>1</sup> Due to the chronic and progressive nature of BPH, many affected men will eventually seek attention and treatment for this complex disorder. Therapy is usually initiated with

medical intervention, and if that fails, minimally invasive interventions or surgical procedures follow. Whereas in the recent past the main emphasis was on improving the bothersome symptoms, the recognition that outcomes such as acute urinary retention (AUR) and the need for surgery are troublesome for patients and costly to the healthcare system has led to an increased emphasis on disease modification and prevention of progression to such outcomes.<sup>2-5</sup>

Of the 2 commonly used pharmacologic interventions for men with symptomatic BPH, 5 $\alpha$ -reductase inhibitors (5ARIs) and  $\alpha_1$ -adrenergic receptor blockers, only the 5ARIs have been shown to modify the underlying pathology. Data from 3 large-scale, randomized clinical studies demonstrated that treatment with the 5ARIs dutasteride or finasteride significantly reduced prostate volume with associated improvements in urinary symptoms and flow, and significant reductions in the risks of AUR- and BPH-related surgery.<sup>6-8</sup> In contrast,  $\alpha_1$ -blockers that reduce the dynamic elements of BPH but do not reduce prostate volume or influence prostate volume increases over time are associated with rapid improvements in symptoms and flow. However, they have not been shown to reduce the long-term risk of AUR- or BPH-related surgery in randomized placebo-controlled studies.<sup>6,8-10</sup> It has been shown that men with larger prostate glands are at greater risk for disease progression as well as AUR and surgery.<sup>11,12</sup> It has therefore been suggested that 5ARIs are most useful in patients presenting with larger glands and higher serum prostate-specific antigen (PSA) values, recognizing the strong clinical correlation between serum PSA level and prostate volume in men with BPH.<sup>13,14</sup>

5ARIs achieve reductions in prostate volume through the inhibition of the steroid 5 $\alpha$ -reductase (5AR)

isoenzymes Type 1 and/or 2, which chemically reduce testosterone to dihydrotestosterone (DHT), the principal androgen that stimulates prostatic growth.<sup>1</sup> This net reduction in androgenic stimulus results ultimately in epithelial atrophy and thus in a reduction in prostate volume by 15% to 25%.<sup>15</sup> Dutasteride is a dual inhibitor of both Type 1 and Type 2 5ARs,<sup>16</sup> whereas finasteride is a selective inhibitor of 5AR Type 2. Dual inhibition of 5AR with dutasteride results in near-complete and consistent suppression of serum DHT, with > 85% of men achieving a  $\geq 90\%$  reduction within 4 weeks.<sup>8</sup> Finasteride suppresses serum DHT by approximately 70%, with approximately half of the treated men achieving this reduction in 1 data series.<sup>17</sup> Until now, the clinical efficacy and safety of dutasteride had been demonstrated in placebo-controlled trials of only 24 months duration<sup>8</sup>; the following report examines the benefits of dutasteride therapy over 48 months in men with LUTS and BPH.

## Methods

ARIA 3001, ARIA 3002, and ARIB 3003 were randomized, double-blind, placebo-controlled studies of the efficacy and safety of dutasteride 0.5 mg once daily for men with symptomatic BPH. The main inclusion criteria included men ages  $\geq 50$  years; diagnosis of BPH by history and physical examination; total prostate volume (TPV)  $\geq 30$  cc, as measured by transrectal ultrasonography; American Urological Association-Symptom Index (AUA-SI) score  $\geq 12$  (moderate-to-severe symptoms); maximal urinary flow rate ( $Q_{max}$ )  $\leq 15$  mL/sec; serum PSA level  $\geq 1.5$  ng/mL; and postvoid residual urine  $< 250$  mL. The reason for the unique criteria of a TPV of  $\geq 30$  mL and serum PSA level  $\geq 1.5$  ng/mL was the recognition that 5ARIs are most suited for such patients. In addition to TPV, transi-

tion zone volume (TZV) was also recorded; however, it was not used as an inclusion criterion. All 3 studies had an optional 2-year open-label extension period in which patients initially receiving dutasteride in the double-blind phase were maintained on dutasteride (D/D group), whereas those initially receiving placebo were offered to switch to open-label dutasteride (P/D group).

At the start of the double-blind phase, patients underwent a 1-month, single-blind placebo run-in period, and were subsequently randomized to treatment with dutasteride 0.5 mg or placebo once daily for 2 years. Safety was assessed through adverse event (AE) reporting, clinical laboratory assessments, and yearly physical examinations, which included focused gynaecomastia evaluations. Data on AUR- and BPH-related surgical events were collected throughout the 4-year period. The data from the 3 trials were pooled for analysis using intention to treat (ITT) analyses. Changes in variables were calculated from baseline. Mean change from baseline or mean percent change from baseline ( $\pm$  standard deviation of the mean) were calculated for continuous parameters (AUA-SI,  $Q_{max}$ , TPV, PSA) at each scheduled time-point in the double-blind and open-label phases. Statistical comparisons between the 2 treatment groups (P/D and D/D) at the scheduled open-label time-points, in terms of the change (or percentage change) from baseline for the continuous parameters, were carried out using a general linear model with effects for baseline, treatment, protocol, and investigator cluster. Statistical comparisons within each of the treatment groups, comparing the difference between the 48 and 24 month values, were carried out using a t-test. Statistical significance was evaluated at the .05 level.

**Table 1**  
Baseline, 24- and 48-Month Parameters for the Open-Label ITT Population

Parameter	Baseline		24 Months		48 Months	
	P/D	D/D	P/D	D/D	P/D	D/D
Serum DHT (pg/mL)	407.0 ± 201.9	427.9 ± 232.1	424.9 ± 194.2	39.1 ± 75.7	29.7 ± 63.0	31.1 ± 60.7
Serum testosterone (pg/mL)	3959 ± 1595	4042 ± 1707	3990 ± 1472	4797 ± 1792	4718 ± 1688	4904 ± 2186
Total prostate volume (cc)	53.9 ± 20.9	56.1 ± 24.2	54.4 ± 25.3	41.3 ± 20.2	42.2 ± 20.2	41.3 ± 23.1
Transition zone volume (cc)	26.9 ± 16.0	28.6 ± 18.0	28.6 ± 19.2	21.5 ± 14.2	22.8 ± 18.8	22.4 ± 16.0
AUA-SI	16.9 ± 5.9	16.6 ± 5.7	14.5 ± 7.2	12.3 ± 6.7	11.3 ± 6.4	10.2 ± 6.1
Q <sub>max</sub> (mL/sec)	10.7 ± 3.7	10.2 ± 3.6	11.3 ± 4.6	12.5 ± 5.6	12.6 ± 5.1	12.8 ± 5.5
Serum PSA (ng/mL)	3.9 ± 2.1	4.1 ± 2.2	4.3 ± 2.8	1.9 ± 1.9	2.0 ± 1.8	1.7 ± 1.8

Data presented as means ± standard deviations. ITT, intention to treat; P/D, placebo/dutasteride-treated subjects; D/D, dutasteride/dutasteride-treated subjects; DHT, dihydrotestosterone; AUA-SI, American Urological Association-Symptom Index; Q<sub>max</sub>, maximal flow rate; PSA, prostate-specific antigen. Reprinted from Debruyne F et al<sup>20</sup> with permission from European Association of Urology.

## Results

A total of 4325 men were randomized into the double-blind phase of the studies: 2158 to placebo and 2167 to dutasteride (Figure 1). For the open-label phase, 2340 patients were enrolled; 1188 had previously received dutasteride (D/D group) and 1152 had previously received placebo (P/D group). Figure 1 shows that for the P/D group, 67% and 70% completed the 2 phases of the study (24 and 48 months, respectively), versus 70% and 73% in the D/D group. Table 1 includes data for patients from the open-label ITT population. No significant differences at the start of the double-blind phase in baseline parameters were observed between patients in the D/D group and those in the P/D group, except for higher mean Q<sub>max</sub> values in the P/D group. To exclude the possibility of responder bias in the open-label extension phase of the study, the characteristics of the men who entered the open-label phase were compared with those who elected not to continue with the study, and were found to be comparable in all parameters (Table 2).

Patients in the D/D group experienced a median decrease in DHT

concentration of 93.7% from baseline to month 24, which was maintained to month 48 (95.3%). Patients in the P/D group had a median 5.9% increase at month 24 and a 95.4% decrease at month 48. At this time-point, 87% of patients in the D/D group and 89% of patients in the P/D group had a reduction in DHT ≥ 90%.

From baseline to month 24, patients

treated with dutasteride had a mean reduction in TPV of 26.0% versus a mean increase of 1.4% for placebo-treated patients ( $P < .001$  between treatment groups) (Figure 2A). At month 48, patients who had been switched from placebo to dutasteride at month 24 (P/D group) had a reduction from baseline in TPV of 21.7%, which was significant versus month 24

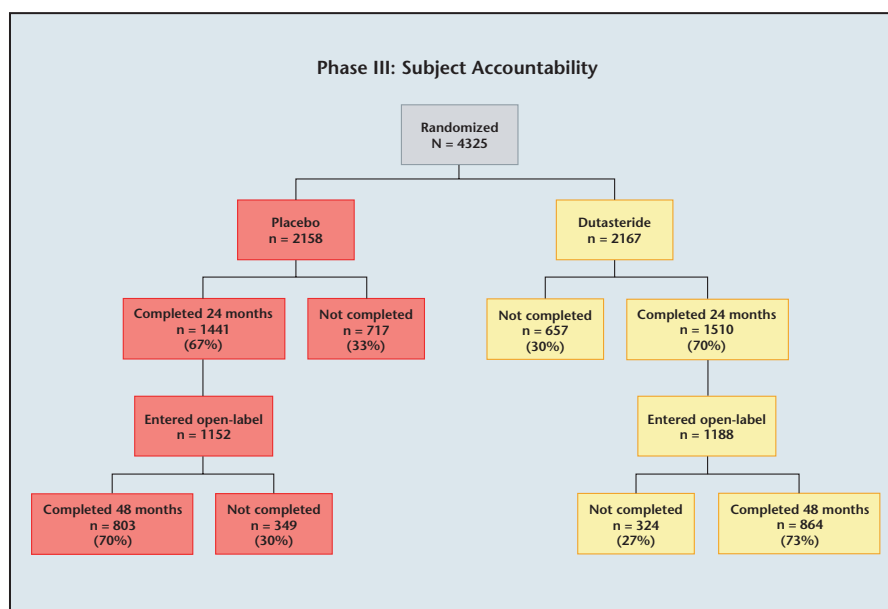


Figure 1. Subject accountability for double-blind and open-label study phases. Adapted from Debruyne F et al<sup>20</sup> with permission from European Association of Urology.

**Table 2**  
Comparison of AUA-SI, Prostate Volume, and  $Q_{\max}$  for Patients Who Entered the Open-Label Phase Versus Those Who Did Not

	Placebo		Dutasteride	
	Entered Open-Label (n = 1152)	Did Not Enter Open-Label (n = 1006)	Entered Open-Label (n = 1188)	Did Not Enter Open-Label (n = 979)
AUA-SI score	14.5 ± 7.16*	15.5 ± 7.56*	12.3 ± 6.68	12.1 ± 6.49
Change in AUA-SI Score from baseline	-2.5 ± 6.67*	-1.6 ± 7.30*	-4.4 ± 6.52	-4.7 ± 6.96
Prostate volume (cc)	54.4 ± 25.31	53.1 ± 24.65	41.3 ± 20.19	40.8 ± 22.24
Change in prostate volume from baseline (%)	1.4 ± 26.16	2.8 ± 24.74	-26.0 ± 19.38	-24.7 ± 21.03
$Q_{\max}$ (mL/sec)	11.3 ± 4.60*	10.9 ± 5.48*	12.5 ± 5.57	12.7 ± 5.75
Change in $Q_{\max}$ (mL/sec)	0.6 ± 4.57	0.9 ± 5.12	2.2 ± 5.15	2.3 ± 5.42

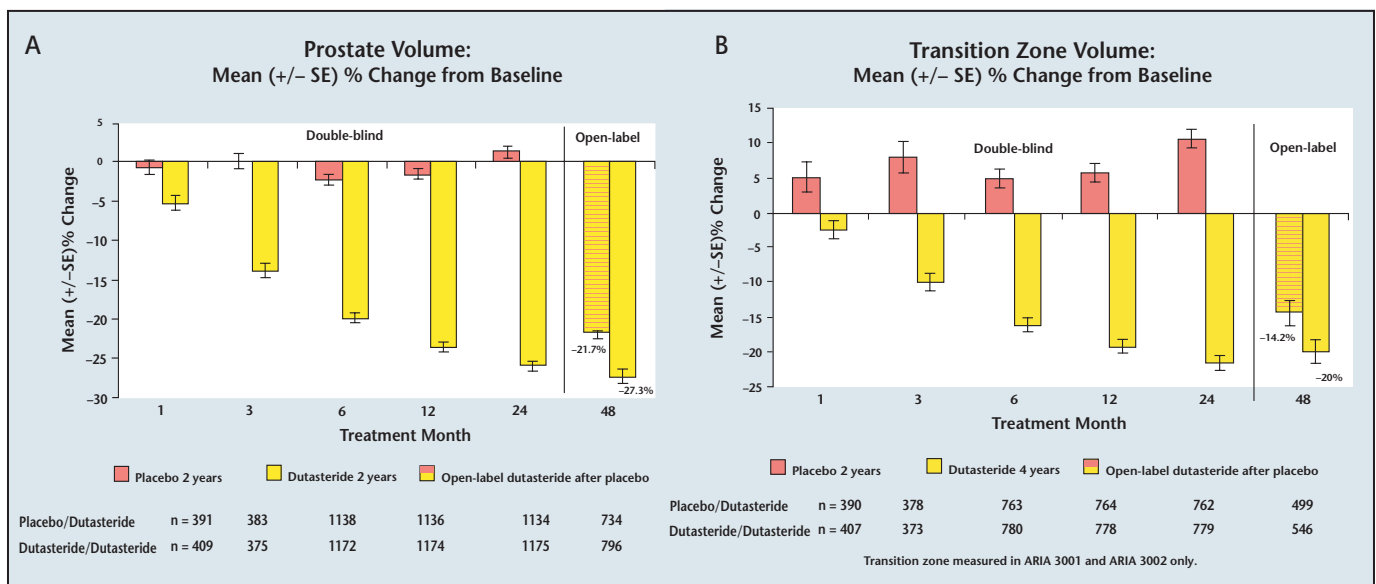
Data are derived from the month 24 visit (double-blind ITT population) and are means ± standard deviations. \* $P < .05$ . AUA-SI, American Urological Association-Symptom Index;  $Q_{\max}$ , maximal flow rate; ITT, intention to treat. Reprinted from Debruyne F et al<sup>20</sup> with permission from European Association of Urology.

( $P < .001$ ). TPV continued to decrease from months 24 to 48 for D/D-treated patients, although this decrease was not statistically significant ( $P = .07$ ). The overall reduction in TPV from baseline to month 48 in D/D-treated patients was significantly greater than that observed in P/D patients (-27.3%,  $P < .001$ ). Transition zone volume

(TZV) decreased in the D/D patients by 20% at 48 months, versus 14.2% in the P/D patients (Figure 2B). However, the P/D-treated patients experienced an increase by nearly 10% from baseline to 24 months prior to being switched to dutasteride.

From baseline to month 24, patients treated with dutasteride had

a mean reduction in AUA-SI score of 4.4 points versus 2.5 points for placebo-treated patients ( $P < .001$  between treatment groups) (Figure 3). At month 48, patients who had been switched from placebo to dutasteride at month 24 (P/D group) had a reduction from baseline in AUA-SI score of 5.6 points, which was signif-



**Figure 2.** Mean change (%) in TPV (A) and TZV (B) from baseline over 48 months. Open bars, placebo/dutasteride-treated subjects (P/D); solid bars, dutasteride/dutasteride-treated subjects (D/D). TPV, total prostate volume; TZV, transition zone volume. Adapted from Debruyne F et al<sup>20</sup> with permission from European Association of Urology.

icant versus month 24 ( $P < .001$ ). AUA-SI score decreased significantly from months 24 to 48 for D/D-treated patients ( $P < .001$ ), with the overall reduction from baseline significantly greater than that observed in patients from the P/D group (6.5 points,  $P < .001$ ).

Figure 4 illustrates the clinical significance of symptom improvement in the ITT population. Figure 4A demonstrates mean changes in symptom score for patients with moderate ( $< 20$  points) versus severe symptoms ( $\geq 20$  points) at baseline. The improvements for men with moderate symptoms ranged from  $-2.7$  to  $-4.9$  points from 12 to 48 months, whereas the men with severe baseline symptoms experienced  $-6.4$  to  $-10.1$  point improvements. When defining an improvement of more than 2 points for men with moderate symptoms and of more than 6 points for men with severe symptoms as significant,<sup>18</sup> up to 74% of all patients in both groups reached this significant symptom improvement at the end of the 48 months of treatment (Figure 4B). Lastly, the proportion of patients with severe symptoms (20 to 35 points) decreased from 42.4% to 8.0% from baseline to month 48, whereas at the end of the study 38.7% of the patients had mild symptoms only (in Figure 4C, patients with mild symptoms at baseline were excluded

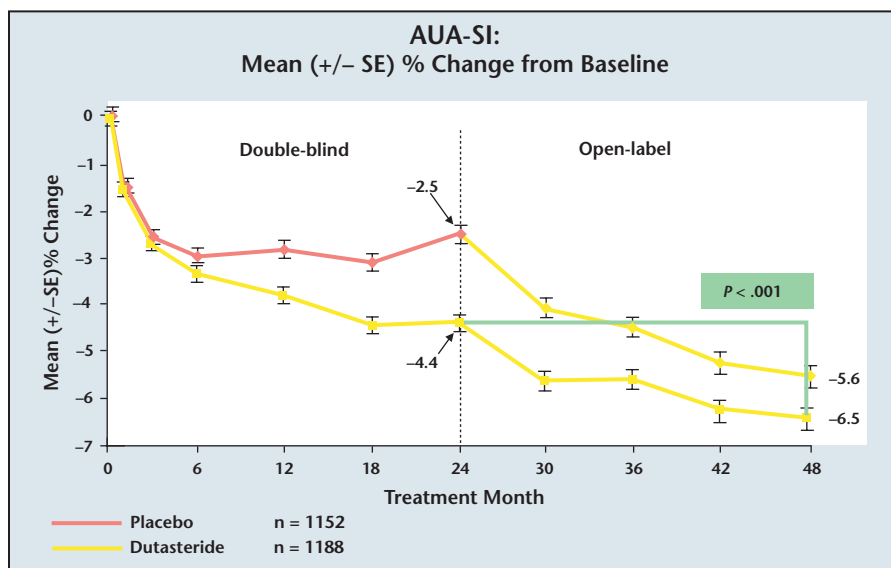


Figure 3. Mean change in AUA-SI scores from baseline over 48 months. Line with diamonds, placebo/dutasteride-treated subjects (P/D); line with squares, dutasteride/dutasteride-treated subjects (D/D). AUA-SI, American Urological Association-Symptom Index; ITT, intention to treat. Adapted from Debruyne F et al<sup>18</sup> with permission from European Association of Urology.

from participation in the trial).

From baseline to month 24, patients treated with dutasteride had a mean improvement in  $Q_{max}$  of 2.2 mL/sec versus 0.6 mL/sec for placebo-treated patients ( $P < .001$  between treatment groups) (Figure 5). At month 48, patients who had been switched from placebo to dutasteride at month 24 (P/D group) had an improvement in  $Q_{max}$  of 1.9 mL/sec, which was significant versus month 24 ( $P < .001$ ).  $Q_{max}$  increased significantly from months 24 to 48 for D/D-treated patients

( $P = .007$ ), with the overall reduction from baseline significantly greater than that observed in patients from the P/D group (2.7 mL/sec,  $P = .042$ ).

Figure 6 illustrates the greater efficacy of dutasteride compared to that of placebo in patients with larger glands and higher serum PSA values. Patients with TPV  $\geq 40$  mL, TZV  $\geq 25$  mL, and serum PSA level  $\geq 3.0$  ng/mL had a greater improvement in symptom score and maximum flow rate after subtracting the placebo effect, compared to those with smaller glands

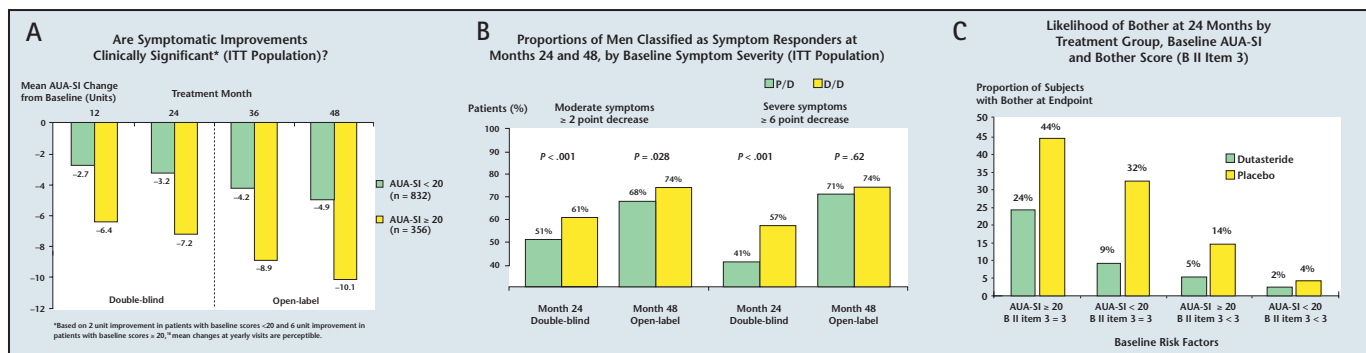


Figure 4. Clinical significance of symptomatic improvement in dutasteride/dutasteride-treated (D/D) patients: (A) mean symptom improvement from baseline for patients with moderate ( $< 20$  points) versus severe ( $\geq 20$  points) from 12 to 48 months; (B) proportion of men with significant improvement of  $\geq 2$  points (moderate at baseline) and  $\geq 6$  points (severe at baseline) at 24 and 48 months; (C) likelihood of bother at 24 months by treatment group, baseline AUA-SI and bother score. ITT, intention to treat; AUA-SI, American Urological Association-Symptom Index; P/D, placebo/dutasteride-treated. Data on file, GlaxoSmithKline.<sup>19</sup>

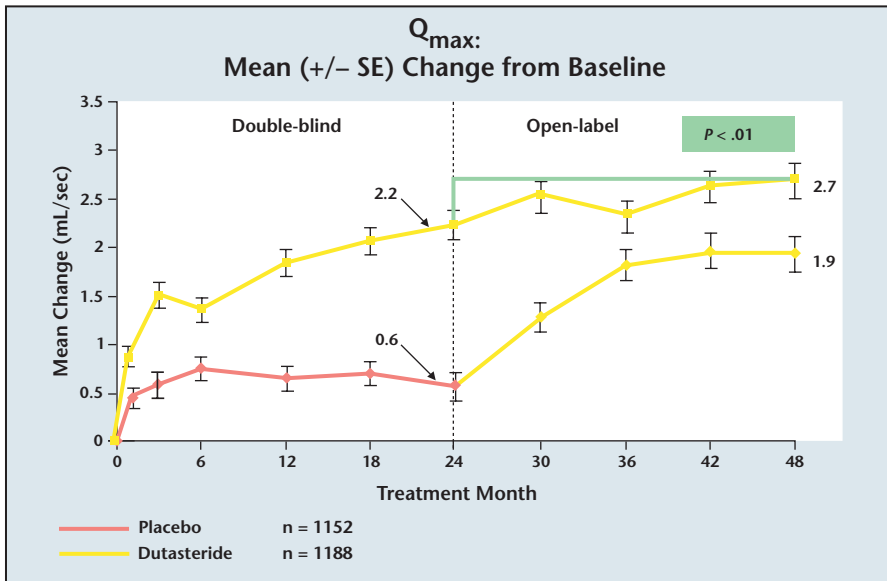


Figure 5. Mean change in  $Q_{max}$  from baseline over 48 months. Line with diamonds, placebo/dutasteride-treated subjects (P/D); line with squares, dutasteride/dutasteride-treated subjects (D/D).  $Q_{max}$ , maximum urinary flow rate. Adapted from Debruyne F et al<sup>10</sup> with permission from European Association of Urology.

and lower PSA values (24 month data from randomized phase of trial).

AUR occurred in 4.6% (placebo) versus 1.9% (dutasteride) of patients in the first 24 months of the placebo-con-

trolled trial for a 57% risk reduction (Figure 7A). After patients switched to open-label dutasteride, the slope of the 2 incidence curves becomes comparable, and at 48 months 6.7% versus

3.3% of patients had experienced AUR. The results regarding surgery for BPH were similar (Figure 7B). At 24 months, 4.4% versus 2.4% (placebo vs dutasteride) underwent surgery, and after patients switched to open-label the incidence curves became parallel, with 5.6% versus 3.3% having had surgery at the end of the 48 months.

The most common drug-related AEs were sexual events (impotence, decreased libido, and ejaculatory disorders) and gynaecomastia (Figures 8A and B). The onset of most new drug-related sexual AEs occurred within the first 6 months of therapy. Among patients who received dutasteride throughout the 48-month study period, the incidence of most drug-related sexual AEs decreased with duration of treatment. The incidence of drug-related gynaecomastia was low and remained constant over the treatment period. Among patients who received dutasteride in the open-label phase only, the incidence of events was similar to those experienced by D/D-treated patients at the start of therapy (Figure 8B). The incidence of events in the P/D group also declined between months 36 and 48 following 1 year of dutasteride therapy. The incidence of drug-related sexual function AEs that led to withdrawal was < 1% in the open-label phase.

Serum PSA level decreased in the D/D group from a mean of 4.1 ng/mL at baseline to 1.9 ng/mL at month 24 (52.9% mean decrease) and 1.7 ng/mL at month 48 (57.2% mean decrease). Patients in the P/D group experienced an average increase in PSA level of 15.0% from a baseline of 3.9 ng/mL to 4.3 ng/mL at month 24. Following initiation of dutasteride treatment at month 24, PSA level was reduced to 2.0 ng/mL at month 48, a mean decrease of 48.4% from baseline.

## Discussion

Treatment with the dual 5ARI dutas-

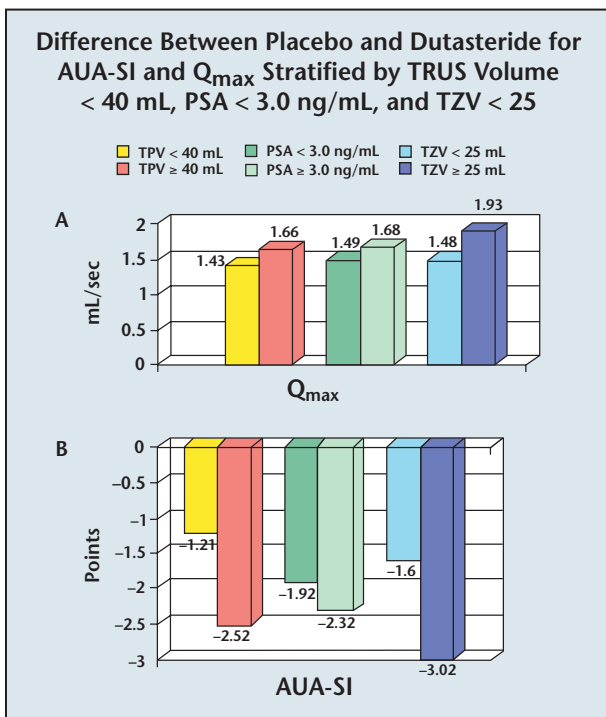


Figure 6. Difference between the average improvement in symptom score (A) and maximum flow rate (B) in placebo- versus dutasteride-treated patients stratified by total prostate volume (< and ≥ 40 mL), transition zone volume (< and ≥ 25 mL), and serum PSA level (< and ≥ 3.0 ng/mL). A greater difference between placebo and dutasteride, ie, a more significant clinical efficacy, is evident for both outcomes and all 3 stratification for the larger glands with higher PSA values. AUA-SI, American Urological Association-Symptom Index;  $Q_{max}$ , maximum urinary flow rate; TRUS, transrectal ultrasound; PSA, prostate-specific antigen; TZV, transition zone volume; TPV, total prostate volume. Data on file, GlaxoSmithKline.<sup>19</sup>

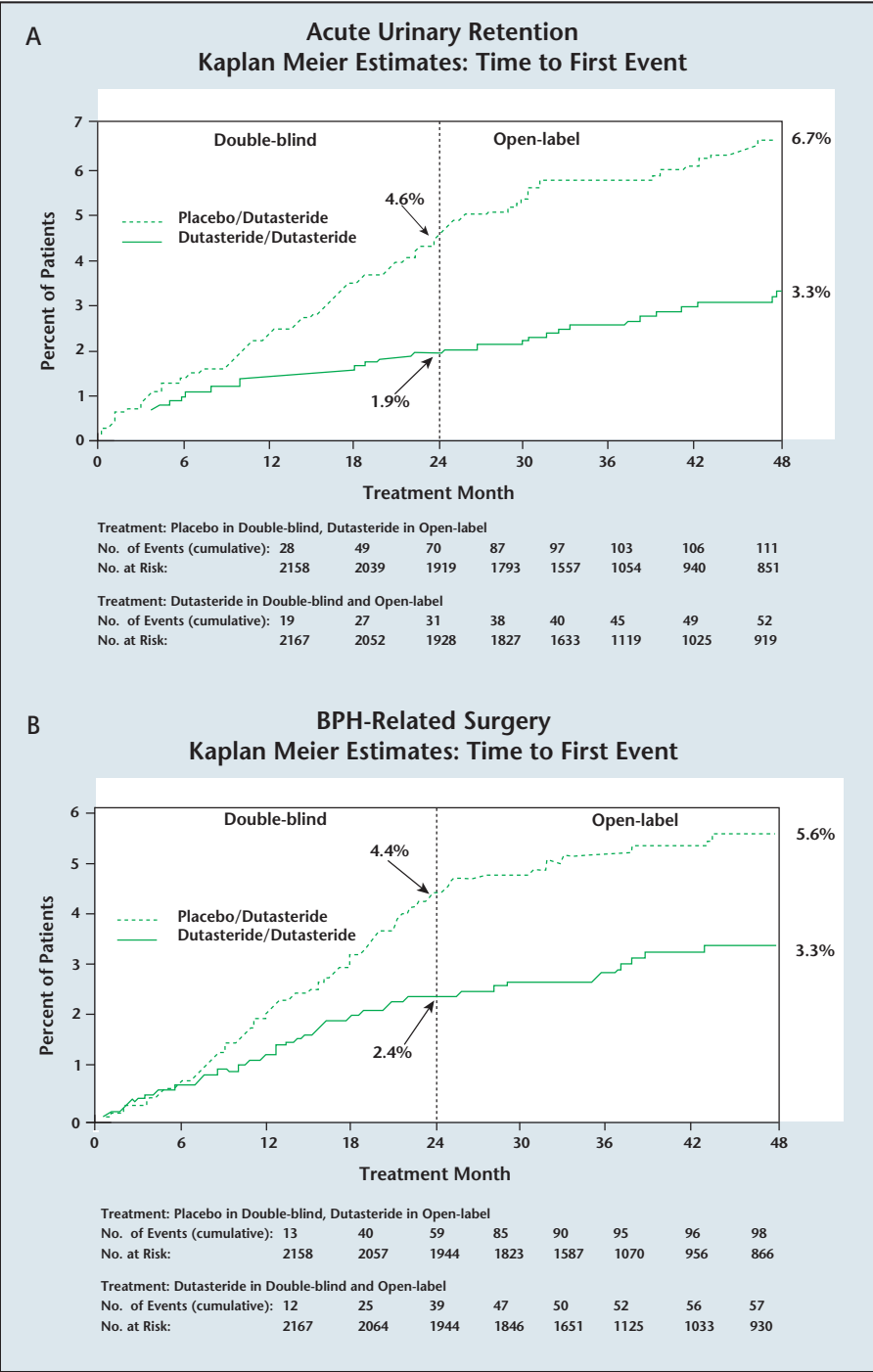


Figure 7. AUR (A) and surgery (B) events for P/D- and D/D-treated patients from baseline to 48 months. AUR, acute urinary retention; P/D, placebo/dutasteride; D/D, dutasteride/dutasteride; BPH, benign prostatic hyperplasia. Data on file, GlaxoSmithKline.<sup>19</sup>

teride for 4 years resulted in sustained and consistent DHT suppression, a continued reduction in total and tran-

sition zone prostate volume, and continued improvements in symptoms and urinary flow. The median reduc-

tion in DHT from baseline was 95.3%, with 87% of patients having a reduction  $\geq 90\%$ . The extent and consistency of these DHT reductions are in accordance with previously published data. Sustained reductions in TPV and TZV occurred in men in the D/D group over 48 months. Although a reduction in TPV between months 24 and 48 was observed in these subjects, it did not reach statistical significance. However, subjects in the D/D group had significantly greater reductions in TPV versus those who received dutasteride for only the latter 24 months, suggesting that for 4 versus 2 years of treatment, a longer duration of therapy increases the likelihood of achieving a maximal reduction in TPV.

Long-term treatment with dutasteride resulted in continued improvements in AUA-SI score and urinary flow. In D/D-treated patients, the change in AUA-SI score from months 24 to 48 was statistically significant. Patients previously receiving placebo during the double-blind phase had a significant improvement in symptom score after receiving 24 months of open-label dutasteride, but this improvement did not achieve the same magnitude as that of the D/D group. The magnitudes of improvement in symptom score from baseline of 4.4 points at month 24 and 6.5 points at month 48 in D/D-treated subjects were in excess of that defined as a clinically relevant decrease in symptoms ( $\geq 3.1$  points).

Over the 4-year period of this study, therefore, a longer duration of dutasteride therapy (4 years) resulted in significantly greater reductions in TPV and improvements in symptoms and urinary flow versus a shorter duration of therapy (2 years). In the longer term, it is possible that the 2 treatment groups may eventually converge with regard to the effect on these parameters. Over this treatment period, how-

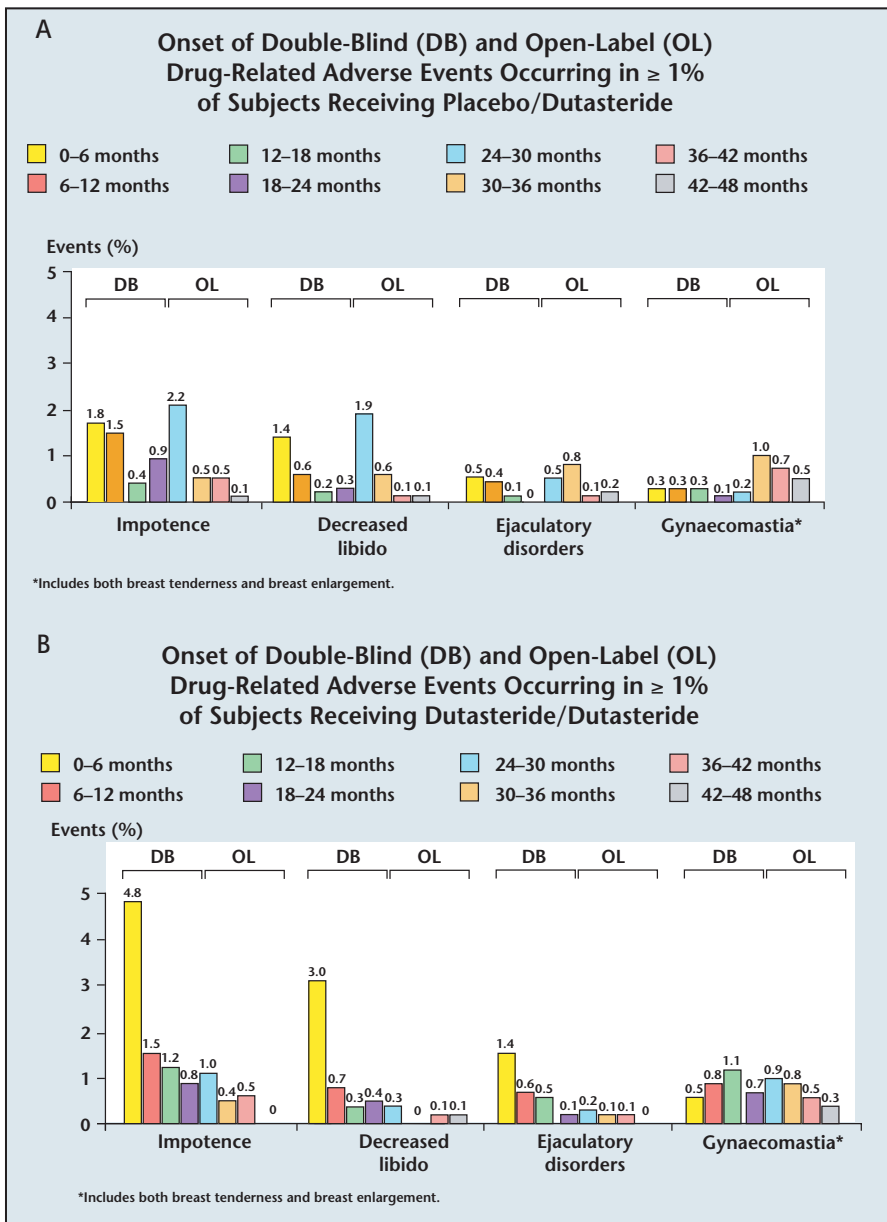


Figure 8. Drug-related adverse events occurring in  $\geq 1\%$  of subjects treated with P/D (A) versus D/D (B): impotence, decreased libido, ejaculatory disorders, and gynaecomastia. P/D, placebo/dutasteride; D/D, dutasteride/dutasteride. Data on file, GlaxoSmithKline.<sup>19</sup>

ever, a longer duration of treatment had a greater effect, with no apparent plateau after 4 years of therapy.

Dutasteride therapy was well tolerated over 4 years and there was a general trend toward a reduction in incidence of the most common sexual AEs over time. The exception was gynaecomastia, the incidence of

which remained low and relatively constant throughout the 4-year period (1.3% in year 1, 1.3% in year 2, 1.8% in year 3, and 0.7% in year 4 for dutasteride-treated patients). Patients initiated on dutasteride therapy after 2 years had a similar pattern of AEs to those starting therapy at baseline, with diminishing incidence over the

24- to 48-month period. Overall, the near maximal suppression of DHT observed with dutasteride does not result in decreased tolerability over a 4-year period.

## Conclusions

In conclusion, long-term treatment with the dual 5ARI dutasteride results in continuing improvements in urinary symptoms and flow rate, and further reductions in TPV in men with symptomatic BPH. The reduction in risk of AUR- and BPH-related surgery, seen in the double-blind phase, was durable over the 4-year term of the studies. These findings establish that the disease-modifying benefits of dutasteride are durable in long-term treatment. Dutasteride was also well tolerated in long-term use, with no new safety issues emerging over 4 years of treatment. ■

## References

- Roehrborn C, McConnell J. Etiology, pathophysiology, epidemiology and natural history of benign prostatic hyperplasia. In: Walsh P, Retik A, Vaughan E, Wein A, eds. *Campbell's Urology*, 8th ed. Philadelphia, PA: Saunders; 2002:1297-1336.
- Jacobsen SJ, Girman CJ, Guess HA, et al. Natural history of prostatism: longitudinal changes in voiding symptoms in community dwelling men. *J Urol*. 1996;155:595-600.
- Lee AJ, Russell EB, Garraway WM, Prescott RJ. Three-year follow-up of a community-based cohort of men with untreated benign prostatic hyperplasia. *Eur Urol*. 1996;30:11-17.
- Flanigan RC, Reda DJ, Wasson JH, et al. 5-year outcome of surgical resection and watchful waiting for men with moderately symptomatic benign prostatic hyperplasia: a Department of Veterans Affairs cooperative study. *J Urol*. 1998;160:12-16; discussion 16-17.
- Anderson JB, Roehrborn CG, Schalken JA, Emberton M. The progression of benign prostatic hyperplasia: examining the evidence and determining the risk. *Eur Urol*. 2001;39:390-399.
- McConnell J, Roehrborn C, Bautista O, et al. The long-term effects of doxazosin, finasteride and the combination on the clinical progression of benign prostatic hyperplasia. *N Engl J Med*. 2003;349:2385-2396.
- McConnell JD, Bruskewitz R, Walsh P, et al. The effect of finasteride on the risk of acute urinary retention and the need for surgical treatment among men with benign prostatic hyperplasia. Finasteride Long-Term Efficacy and Safety Study Group. *N Engl J Med*. 1998;338:557-563.
- Roehrborn CG, Boyle P, Nickel JC, et al. Efficacy and safety of a dual inhibitor of 5-alpha-reductase types 1 and 2 (dutasteride) in men with

- benign prostatic hyperplasia. *Urology*. 2002;60:434-441.
9. Djavan B, Marberger M. A meta-analysis on the efficacy and tolerability of alpha1-adrenoceptor antagonists in patients with lower urinary tract symptoms suggestive of benign prostatic obstruction. *Eur Urol*. 1999;36:1-13.
  10. Roehrborn CG. Are all alpha-blockers created equal? An update. *Urology*. 2002;59(suppl 1):3-6.
  11. Roehrborn CG, Boyle P, Bergner D, et al. Serum prostate-specific antigen and prostate volume predict long-term changes in symptoms and flow rate: results of a four-year, randomized trial comparing finasteride versus placebo. PLESS Study Group. *Urology*. 1999;54:662-669.
  12. Roehrborn CG, McConnell JD, Lieber M, et al. Serum prostate-specific antigen concentration is a powerful predictor of acute urinary retention and need for surgery in men with clinical benign prostatic hyperplasia. PLESS Study Group. *Urology*. 1999;53:473-480.
  13. Roehrborn CG, Boyle P, Gould AL, Waldstreicher J. Serum prostate-specific antigen as a predictor of prostate volume in men with benign prostatic hyperplasia. *Urology*. 1999;53:581-589.
  14. Boyle P, Gould AL, Roehrborn CG. Prostate volume predicts outcome of treatment of benign prostatic hyperplasia with finasteride: meta-analysis of randomized clinical trials. *Urology*. 1996;48:398-405.
  15. Marks LS, Partin AW, Dorey FJ, et al. Long-term effects of finasteride on prostate tissue composition. *Urology*. 1999;53:574-580.
  16. Bramson HN, Hermann D, Batchelor KW, et al. Unique preclinical characteristics of GG745, a potent dual inhibitor of 5AR. *J Pharmacol Exp Ther*. 1997;282:1496-1502.
  17. McConnell JD, Wilson JD, George FW, et al. Finasteride, an inhibitor of 5 alpha-reductase, suppresses prostatic dihydrotestosterone in men with benign prostatic hyperplasia. *J Clin Endocrinol Metab*. 1992;74:505-508.
  18. Barry MJ, Williford WO, Chang Y, et al. Benign prostatic hyperplasia specific health status measures in clinical research: how much change in the American Urological Association symptom index and the benign prostatic hyperplasia impact index is perceptible to patients? *J Urol*. 1995;154:1770-1774.
  19. GlaxoSmithKline. Philadelphia, PA.
  20. Debruyne F, Barkin J, van Erps P, et al.; ARIA3001, ARIA3002, ARIB3003 Study Investigators. Efficacy and safety of long-term treatment with the dual 5 alpha-reductase inhibitor dutasteride in men with symptomatic benign prostatic hyperplasia. *Eur Urol*. 2004;46:488-494.

## Main Points

- Outcomes of benign prostatic hyperplasia (BPH) and lower urinary tract symptoms, such as acute urinary retention (AUR) and the need for surgery, have led to an increased emphasis on disease modification and prevention of progression.
- 5 $\alpha$ -reductase inhibitors such as dutasteride and finasteride have been shown to modify the underlying pathology of symptomatic BPH, resulting in significant reductions in prostate volume and in the risks of AUR- and BPH-related surgery. They have also demonstrated improvements in urinary symptoms and flow.
- Three randomized, double-blind, placebo-controlled studies were performed to test the efficacy and safety of dutasteride 0.5 mg once daily in the treatment of men with symptomatic BPH. All had an optional 2-year open-label extension period in which patients initially receiving dutasteride in the double-blind phase were maintained on dutasteride, whereas those initially receiving placebo were permitted to switch to open-label dutasteride.
- Over the 4-year study period, a longer duration of dutasteride therapy resulted in significantly greater reductions in total prostate volume and improvements in symptoms and urinary flow versus a shorter duration of therapy (2 years), with no apparent plateau.
- Dutasteride therapy was well tolerated over 4 years, and there was a general trend toward a reduction in incidence of the most common sexual adverse events over time.